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ACUTE TOXICITY EVALUATION OF HALON REPLACEMENT TRIFLUOROIODOMETHANE (CF_3I)

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TECHNICAL REVIEW AND APPROVAL

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

Terry A. Childress

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Trifluoroiodomethane (CF_3I) is being considered as a replacement compound for Halon 1301. The material would be used as a flooding agent for in-flight aircraft and electronic equipment fires and for fire extinguishment in confined spaces. A series of 4-h nose-only inhalation exposures were performed on F-344 rats at 1.0 and 0.5% CF_3I. No signs of toxic stress were noted during or following exposure. Inhalation of CF_3I at concentrations of 1.0 or 0.5% in the atmosphere did not result in any observable toxicological effects.

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PREFACE

This is one of a series of technical reports describing results of the experimental laboratory programs conducted at the Toxic Hazards Research Unit, ManTech Environmental Technology, Inc. This document serves as a final report on the acute toxicity evaluation of halon replacement trifluoroiodomethane (CF_3I). The research described in this report began in August 1993 and was completed in September 1993 under Department of the Air Force Contract No. F33615-90-C-0532 (Study No. F25). Lt Col Terry A. Childress served as Contract Technical Monitor for the U.S. Air Force, Armstrong Laboratory.

The animals used in this study were handled in accordance with the principles stated in the *Guide for the Care and Use of Laboratory Animals*, prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, Department of Health and Human Services, National Institute of Health Publication #86-23, 1985, and the Animal Welfare Act of 1966, as amended.

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ABBREVIATIONS

A/G	Albumin/globulin ratio
ALT	Alanine amniotransferase
AST	Aspartate amniotransferase
BW	Body weight
°C	Degrees centigrade
CF_3I	Trifluoroiodomethane
dL	Decaliter
F-344	Fischer 344 rats
fl	Fentaliter
g	Gram
h	Hour
HCT	Hematocrit
HGB	Hemoglobin
IU	International units
m	Meter
MBW	Mean body weight
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mm	Millimeter
N	Number
pg	Picogram
ppm	Parts per million
RBC	Red blood cell
SEM	Standard error of the mean
T_4	Thyroxine
TBG	Thyroxine-binding globulin
WBC	White blood cell

SECTION 1
INTRODUCTION

Environmental concern over the depletion of stratospheric ozone and global warming has led to an international treaty called the Montreal Protocol (1987), which calls for the phase out of halons by the Year 2000. Presently, the Air Force is using Halon 1301 as a flooding agent for extinguishing in-flight aircraft and electronic equipment fires and for fire extinguishment in confined spaces. Because it is believed to have less ozone-depleting activity, trifluoroiodomethane (CF_3I) is being considered as a possible replacement for Halon 1301.

Trifluoroiodomethane is not a commercial product, therefore, very little is known concerning its toxicological properties. However, based on available data from similar compounds, the inhalation LC_{50} should be quite high (greater than 10%). Because the compound has an iodine atom, it is possible that exposure might interfere with thyroid function (Thomas and Bell, 1982). To determine if inhalation of CF_3I causes changes in the thyroid or thyroid function, inhalation exposures were performed in rats, in which the thyroid hormone (thyroxine [T_4]) was monitored during the postexposure period. Two concentrations were tested with subsequent clinical chemistry evaluations performed immediately following exposure, 3 and 14 days postexposure.

Because CF_3I is not being produced commercially at this time, it is scarce and relatively expensive. To reduce the amount of test compound required to perform these toxicologic evaluations, a nose-only chamber was employed. Chamber volume and air flow are greatly reduced using this apparatus compared to a whole-body exposure system, resulting in the use of smaller quantities of the test material.

This study was intended to evaluate the potential toxicity of CF_3I following short-term, high-concentration inhalation exposures in rats. It was also designed to determine if changes in the endocrine system occurred following the inhalation exposure regimen.

SECTION 2
MATERIALS AND METHODS

Test Compound

The CF_3I (CAS 2314-97-8) used in this study was purchased from PCR, Inc., Gainesville, FL. The compound has a formula weight of 195.91 and a boiling point of -22.5 °C. The compound is a liquid and is stored in a cylinder under pressure.

Test Animals

Ninety male Fischer 344 (F-344) rats were purchased from Charles River Breeding Laboratories, Raleigh, NC. The rats were 6 weeks of age upon arrival and 8 weeks of age at the time of exposure. All rats were identified by tail tattoo and were subjected to a 2-week quarantine period. Water and feed (Purina Formulab #5008) were available ad libitum, except during exposure. Animal room temperatures were maintained at 21 to 25 °C, and the light/dark cycle was set at 12-h intervals. The animals were group housed (2 per cage, except during exposure) in clear plastic cages with wood chip bedding (Betta-Chip, Northeastern Products Corp., Warrensburg, NY). The animals used in this study were handled in accordance with the principles stated in the *Guide for the Care and Use of Laboratory Animals*, prepared by the U.S. Department of Health and Human Services (1985).

Generation and Analysis of Exposure Atmospheres

Trifluoroiodomethane vapor was generated from a cylinder partially submersed in a controlled water bath maintained at 22 °C. The vapor concentration was controlled using a calibrated Matheson rotameter (Matheson Gas Products, Secaucus, NJ) to measure the volume of gas delivered to a known volume-dilution air input stream. The chamber atmosphere was analyzed using a Varian 3400 gas chromatograph (Varian Associates, Palo Alto, CA) equipped with a loop injection system with a flame ionizing detector. A 15-m x 0.53-mm wide bore, fused silica capillary column coated with SPB-5 was used. The column temperature was isothermal at 50 °C. The analysis samples were taken from a centrally located port. The system was programmed to inject once per minute and cycle every 5 min followed by integration, printout of area data, and start of a new cycle. This method provided for near continuous analysis of the exposure chamber atmosphere.

The nose-only chamber is a stainless-steel flow past chamber as described by Cannon et al., 1983. The chamber has 52 ports; 30 were randomly selected for rat exposure. Plexiglas rat restraining tubes that extended radially outward were plugged into the ports.

Exposure Regimen

Each nose-only exposure duration was for 4-h. The exposure groups of 30 rats each were divided into 2 interim sacrifice groups and 1 final sacrifice group of 10 rats each. Interim sacrifices occurred immediately following exposure and at 3 days postexposure. A final sacrifice occurred at 14 days postexposure. A total of 30 F-344 rats were included in each of 3 exposures, at 1.00%, 0.50%, and an air control.

Toxicity Assessments

Records were maintained of body weights (BW), signs of toxicity, and mortality. Euthanasia was via halothane inhalation overdose. At sacrifice, gross pathology was performed on all animals, and tissues were harvested for histopathologic examination (Table 1). Tissues were fixed in 10% neutral buffered formalin, trimmed, and further processed via routine methods for hematoxylin-eosin-stained paraffin-embedded sections (Luna, 1968). Additionally, blood was drawn for select hematology and clinical chemistry assays (Table 2). Erythrocytes were enumerated on a Coulter counter (Coulter Electronics, Hialeah, FL), and sera for clinical chemistry evaluations were assayed on an Ektachem 700XR (Eastman Kodak, Rochester, NY). Thyroxine and thyroxine-binding globulin (TBG) assays were performed using a DuPont ACA analyzer (DuPont Co., Wilmington, DE).

Statistical Analysis

Comparisons of postexposure BW gains were performed using the repeated multivariate analysis of variance with Scheffe pairwise comparisons (Barcikowski, 1983). A two-factorial (dose and time) analysis of variance with multivariate comparisons was used to analyze the hematology and clinical chemistry data. Histopathology results were analyzed using the Fischer's Exact Test (Zar, 1974).

TABLE 1. TISSUES HARVESTED FROM CONTROL AND CF_3I-EXPOSED F-344 RATS FOR HISTOPATHOLOGIC EXAMINATION

Gross Lesions	Spleen
Heart	Thyroid
Lungs	Kidneys
Trachea	Adrenals
Liver	Nasal Cavity
Parathyroid	

TABLE 2. SERUM CHEMISTRY AND WHOLE BLOOD ASSESSMENTS FROM CONTROL AND CF_3I-EXPOSED F-344 RATS

Albumin
Thyroxine-binding globulin (TBG)
Thyroxine (T_4)
Alanine aminotransaminase (ALT)
Aspartate aminotransaminase (AST)
Globulin
Hematocrit (HCT)
Hemoglobin
Red blood cell (RBC) count
Total and differential leukocyte count

SECTION 3
RESULTS

Exposure System Analysis

The specified target concentrations of 1.00 and 0.50% CF_3I were maintained during the 4-h exposure period. The exposure mean concentrations were maintained within ± 6% of the desired concentrations. Mean concentrations for each exposure, along with the mean high and low concentrations, are provided in Table 3.

Inhalation Toxicity

There were no deaths resulting from exposure. No treatment-related signs of toxic stress were noted during exposure or during the 14-day observation period. Comparison of the mean body weights (MBW) of the control and high-exposure groups indicated an initial loss in the CF_3I group at 24 h followed by normal gains thereafter (Table 4). A similar loss in MBW was noted in the low-exposure group at 24 h, however, the MBW of this group continued to be less than the MBW of the other two groups throughout the 14-day postexposure observation period.

TABLE 3. ANALYSIS OF CF_3I CONCENTRATIONS INHALED BY MALE F-344 RATS

Target Concentration (%)	1.00	0.50
Mean Concentration (%)	0.99	0.53
Standard Deviation	0.01	0.01
Maximum Concentration (%)	1.01	0.56
Minimum Concentration (%)	0.930	0.52

TABLE 4. MEAN[a] BODY WEIGHTS OF MALE F-344 RATS EXPOSED TO CF_3I VIA NOSE-ONLY INHALATION

	Day (Pre- and Postexposure)			
	0	**1**	**7**	**14**
High Exposure	182.1 ± 2.2	178.7 ± 2.8	209.7 ± 2.4	228.4 ± 3.3
Low Exposure	187.0 ± 1.8	180.2 ± 2.0	196.8 ± 3.4	210.1 ± 3.4
Control	183.3 ± 2.1	182.5 ± 2.0	203.2 ± 3.0	222.3 ± 3.4

[a]Mean ± SEM, N=30 at Day 0, N=20 at Day 1, N=10 at Days 7 and 14.

The results of the hematology and clinical chemistry analyses are listed in Tables 5 and 6. Several blood parameters were found to be statistically different from control values, however, all values were within normal limits for F-344 rats. The mean TBG and T_4 values of the high-exposure group were statistically significantly different from the control values at 14-days postexposure. Also, the mean TBG value of the low-exposure group was different from the control group immediately following exposure. All mean values were within normal limits and not considered treatment related. Tissues examined microscopically showed no lesions of clinical or pathological significance.

TABLE 5. MEAN[a] HEMATOLOGIC AND CLINICAL CHEMISTRY VALUES OF MALE RATS SACRIFICED POSTEXPOSURE FOLLOWING A 4-H NOSE-ONLY EXPOSURE TO CF_3I

	0 H Postexposure		3 Days Postexposure	
	High 1.0%	Control	High 1.0%	Control
RBC ($X10^6/\mu L$)	7.4 ± 0.1	7.3 ± 0.2[d]	7.5 ± 0.1	7.9 ± 0.1
WBC ($X10^3/\mu L$)	3.7 ± 0.2	3.4 ± 0.2[d]	6.2 ± 0.2	6.2 ± 0.2
HCT (%)	41.7 ± 0.5	41.0 ± 1.1[d]	42.8 ± 0.8	43.7 ± 0.6
HGB (g/dL)	13.3 ± 0.2	13.1 ± 0.3[d]	13.0 ± 0.2[c]	14.1 ± 0.2
Total Protein (g/dL)	5.8 ± ⟨0.1	6.1 ± 0.1	6.2 ± 0.1	6.2 ± ⟨0.1
Albumin (g/dL)	3.1 ± ⟨0.1	3.3 ± ⟨0.1	3.4 ± ⟨0.1	3.4 ± ⟨0.1
Globulin (g/dL)	2.7 ± ⟨0.1	2.8 ± ⟨0.1	2.8 ± ⟨0.1	2.8 ± ⟨0.1
A/G ratio	1.1 ± ⟨0.1[b]	1.2 ± ⟨0.1	1.2 ± ⟨0.1	1.2 ± ⟨0.1
AST (IU/L)	94.9 ± 5.0	104.5 ± 8.1	160.4 ± 16.1[b]	76.0 ± 1.3
ALT (IU/L)	55.7 ± 1.3[b]	66.8 ± 2.3	58.8 ± 1.0	63.1 ± 1.6
TBG	37.7 ± 0.3	36.0 ± 0.5	39.3 ± 0.2	32.9 ± 0.8
T_4	3.6 ± 0.1	2.9 ± 0.3	4.5 ± 0.3	3.6 ± 0.4
MCV (fl)	56.7 ± 0.2	56.2 ± 0.4[d]	56.9 ± 0.3	55.1 ± 0.1
MCH (pg)	18.1 ± ⟨0.1	18.0 ± 0.1[d]	17.3 ± 0.4	17.7 ± 0.1
MCHC (g/dL)	31.9 ± 0.1	32.0 ± 0.1[d]	30.3 ± 0.7[b]	32.2 ± 0.1

(continued)

TABLE 5. Continued

	14 Days Postexposure	
	High 1.0%	Control
RBC ($X10^6/\mu L$)	8.2 ± 0.1	8.4 ± 0.1
WBC ($X10^3/\mu L$)	5.7 ± 0.2[c]	6.7 ± 0.3
HCT (%)	44.9 ± 0.4	45.2 ± 0.3
HGB (g/dL)	14.5 ± 0.1	15.0 ± 0.1
Total Protein (g/dL)	6.4 ± ⟨0.1[b]	5.2 ± 0.1
Albumin (g/dL)	3.5 ± ⟨0.1[b]	3.3 ± ⟨0.1
Globulin (g/dL)	2.9 ± ⟨0.1	1.9 ± ⟨0.1
A/G ratio	1.2 ± ⟨0.1[b]	1.7 ± ⟨0.1
AST (IU/L)	100.1 ± 4.6	85.8 ± 1.3
ALT (IU/L)	63.3 ± 1.2[b]	54.5 ± 1.4
TBG	34.1 ± 0.7[b]	38.8 ± 0.5
T_4	4.3 ± 0.4[b]	2.4 ± 0.2
MCV (fl)	54.6 ± 0.2	53.5 ± 0.1
MCH (pg)	17.7 ± 0.1	17.8 ± 0.1
MCHC (g/dL)	32.4 ± 0.1	33.2 ± 0.1

[a]Mean ± SEM, N=10.
[b]Significantly different than control at p⟨0.01.
[c]Significantly different than control at p⟨0.05.
[d]N=9.

TABLE 6. MEAN[a] HEMATOLOGIC AND CLINICAL CHEMISTRY VALUES OF MALE RATS SACRIFICED POSTEXPOSURE FOLLOWING A 4-H NOSE-ONLY EXPOSURE TO CF_3I

	0 H Postexposure		3 Days Postexposure	
	Low 0.5%	Control	Low 0.5%	Control
RBC ($X10^6/\mu L$)	7.6 ± 0.1	7.6 ± 0.2[c]	7.6 ± 0.1	7.9 ± 0.1
WBC ($X10^3/\mu L$)	3.8 ± 0.2	3.4 ± 0.2[c]	5.6 ± 0.1	6.2 ± 0.2
HCT (%)	42.8 ± 0.8	41.0 ± 1.1[c]	42.3 ± 0.3	43.7 ± 0.6
HGB (g/dL)	13.7 ± 0.2	13.1 ± 0.3[c]	13.6 ± 0.1	14.1 ± 0.2
Total Protein (g/dL)	6.2 ± 0.1	6.1 ± 0.1	6.3 ± 0.1	6.2 ± ⟨0.1
Albumin (g/dL)	3.4 ± 0.1	3.3 ± ⟨0.1	3.5 ± ⟨0.1	3.4 ± ⟨0.1
Globulin (g/dL)	2.8 ± ⟨0.1	2.8 ± ⟨0.1	2.8 ± ⟨0.1	2.8 ± ⟨0.1
A/G ratio	1.2 ± ⟨0.1	1.2 ± ⟨0.1	1.2 ± ⟨0.1	1.2 ± ⟨0.1
AST (IU/L)	112.2 ± 5.1	104.5 ± 8.1	76.0 ± 1.3	76.0 ± 1.3
ALT (IU/L)	71.9 ± 1.4	66.8 ± 2.3	60.0 ± 1.0	63.1 ± 1.6
TBG	32.6 ± 0.8[b]	36.0 ± 0.5	38.1 ± 0.4	32.9 ± 0.8
T_4	3.9 ± 0.3	2.9 ± 0.3	2.4 ± 0.3	3.6 ± 0.4
MCV (fl)	56.2 ± 0.3	56.2 ± 0.4[c]	56.0 ± 0.2	55.1 ± 0.1
MCH (pg)	17.9 ± 0.1	18.0 ± 0.1[c]	18.0 ± 0.1	17.7 ± 0.1
MCHC (g/dL)	31.9 ± 0.2	32.0 ± 0.1[c]	32.1 ± 0.1	32.2 ± 0.1

(continued)

TABLE 6. Continued

	14 Days Postexposure	
	Low 0.5%	Control
RBC ($X10^6/\mu L$)	8.3 ± 0.1	8.4 ± 0.1
WBC ($X10^3/\mu L$)	6.4 ± 0.3	6.7 ± 0.3
HCT (%)	44.3 ± 0.6	45.2 ± 0.3
HGB (g/dL)	14.9 ± 0.2	15.0 ± 0.1
Total Protein (g/dL)	5.4 ± 0.1	5.2 ± 0.1
Albumin (g/dL)	3.3 ± ⟨0.1	3.3 ± ⟨0.1
Globulin (g/dL)	2.1 ± ⟨0.1[b]	1.9 ± ⟨0.1
A/G ratio	1.6 ± ⟨0.1	1.7 ± ⟨0.1
AST (IU/L)	95.9 ± 3.3	85.8 ± 1.3
ALT (IU/L)	58.0 ± 1.6	54.5 ± 1.4
TBG	40.5 ± 1.0	38.8 ± 0.5
T_4	2.4 ± 0.2	2.4 ± 0.2
MCV (fl)	53.4 ± 0.2	53.5 ± 0.1
MCH (pg)	18.0 ± 0.1	17.8 ± 0.1
MCHC (g/dL)	33.7 ± 0.1	33.2 ± 0.1

[a]Mean ± SEM, N=10.
[b]Significantly different than control at $p\langle 0.05$.
[c]N=9.

SECTION 4
DISCUSSION

Acute (4-h) inhalation of CF_3I at concentrations of 1.0 and 0.5% did not result in any signs of toxic stress during or following exposure. Histopathologic examination of tissues sampled at different time points following exposure indicated normal findings. Clinical chemistry assays following exposure showed no biologically significant differences in thyroid hormones in the circulating blood of CF_3I-treated rats when compared to control rats.

The lack of mortality in rats exposed to 10,000 ppm (1%) CF_3I would indicate that the compound could be classified as "practically non-toxic" (Deickmann and Gerarde, 1969). However, because of its extremely high vapor pressure, a greater hazard might be that of asphyxiation, if large quantities of this material were to be spilled in a confined area.

SECTION 5

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